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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/681,669 | 10/07/2003 | Arthur J. Blume | 2598-4000US4 | 7579 |

27123 7590 06/14/2006

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| EXAMINER | |
|---|---|
| TUNGATURTHI, PARITHOSH K | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/681,669 | BLUME, ARTHUR J. | |
| | Examiner | Art Unit | |
| | Parithosh K. Tungaturthi | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 47-50 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 47-50 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 06.04.2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election of Group III, claims 47-50 in the reply filed on 04/03/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

2. Claims 1-46 and 51-75 have been cancelled.

3. Claims 47-50 are under examination.

### *Priority*

4. The instant application claims priority to U.S. Application # 08/286,084, filed August 3, 1994. However, the U.S. Application # 08/286,084 does not contain the subject matter as claimed in the instant claims, for example "rVab" or "rVab-Pep". Hence, the instant application is given the priority of U.S. Patent 6010861, which was field on 06/07/1995. Appropriate correction is required.

The applicant is further requested to correct the priority information in the first line of the specification.

### *Claim Rejections - 35 USC § 112*

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 47-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 47 and 48 are vague and indefinite in the recitation of "rVab" as the sole means of identifying the expressed gene referred to in claims 47 and 48. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. Amending the claims to specifically and uniquely identify rVab, for example, by SEQ ID NO can obviate this rejection.

Claim 47 is further vague and indefinite for reciting "a reporter of binding of a ligand to a determinant of a pharmacological target" because the exact meaning of the phrase unclear. It is confusing as to what the invention is intended to be. What does the "reporter of a binding ligand to a determinant of a target mean"? Does the applicant mean that the reporter is necessary for the ligand to be expressed? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Further, the claim is indefinite for reciting "at least two determinants". The claim is confusing because it is not clear as to what is meant by determinant. Is the determinant an effector, is it a binding site, is it functional, etc., ?

Further, the claim is vague for reciting "which target requires binding of ligand to at least two determinants of said target to produce a biological response" because it is

not clear as to what determinants the applicant is referring to? Is the applicant referring to two different epitopes of the same antigen? Further, it is indefinite in the recitation of "biological response" because the claim, as written does not clearly specify the biological activity that is being referred to.

In addition, the claim is confusing for reciting "said reporter comprising an rVab portion of an component of said rVab Pep .....wherein said rVab component of said rVab Pep.....", because it is not clear as to if the "rVab portion" is the same as "rVab component". Further, is the "Pep" same as the peptide portion in "rVab Pep". If not, what is it the difference? If they are the same, please designate identical names to avoid any confusion.

As mentioned earlier, claim 47 is drawn to "a reporter of binding of a ligand.....second determinant of said target". Does the applicant mean that the single chain polypeptide (as mentioned below) serves as a "reporter system" in determining the various determinants of the pharmaceutical target? Or is there a reporter system that has to be present to activate the synthesis of the claimed product? The applicant is required to clarify the invention.

Due to the indefinite nature of the claims, the claims interpreted as any antibody conjugated to any peptide molecule wherein both the antibody and the peptide bind to the same target, wherein the peptide molecule is conjugated to either or both the amino terminus of VH region or the carboxy terminus of the CL region.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 47, 48 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Shin and Morrison (Proc. Natl. Acad Sci USA. 1990. 87:5322-5326).

As mentioned earlier, due to the indefinite nature of the claims, the claims interpreted as any antibody conjugated to any peptide molecule wherein both the antibody and the peptide bind to the same target, wherein the peptide molecule is conjugated to the carboxy terminus of the CL region.

Shin and Morrison teach the expression and characterization of an antibody binding specificity joined to insulin-like growth factor 1 and the potential applications of such chimeric molecules for cellular targteting (title, in particular). Shin and Morrison teach a chimeric molecules comprising IgG3-IGF1, wherein IGF1 is an insulin-like growth factor and IgG3 is the chimeric mouse-human anti-dansyl (anti-Dns) antibody (abstract, in particular). Shin and Morrison teach that the simultaneous binding by the antibody combining sire to the antigen on the surface of the tumor cell and by the hormone to the hormone receptor will increase the specificity of targeting (page 5325 column 2, in particular). Shin and Morrison teach IgG3-IGF1 chimeric protein that retain their specificity for the antigen Dns and the IGF1 receptor on the same target cell.

Further Shin and Morrison teach that the IGF1 molecule can be conjugated to the C-terminus of the of the CL region (please see figure 2C, page 5324 in particular).

Thus, since the claims are drawn to any antibody conjugated to any peptide molecule wherein both the antibody and the peptide bind to the same target and since Shin and Morrison teach a chimeric protein comprising IgG3-IGF1; wherein IgG3 molecule is the anti-Dns antibody and IGF1 receptor is an insulin-like growth factor (a 7 kDa molecule, which is less than 100 amino acids in length and can be categorized as a peptide) that retain their specificity for the antigen Dns and the IGF1 receptor on the same target cell, the teachings of Shin and Morrison read upon the claimed invention as interpreted.

Therefore, Shi and Morrison anticipate the claimed invention.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shin and Morrison (Proc. Natl. Acad Sci USA. 1990. 87:5322-5326) in view of George et al (Journal of Immunology. 1994, 152:1802).

Claims 47, 48 and 50 are described supra. Further, as mentioned earlier due to the indefinite nature of the claims, claim 49 is interpreted as any antibody conjugated to any peptide molecule wherein both the antibody and the peptide bind to the same target, wherein the peptide molecule is conjugated to the amino terminus of VH region.

Shin and Morrison et al has been described supra. Shin and Morrison does not teach the conjugation of the peptide molecule to the N-terminus of the VH region of antibody. These deficiencies are made up for by George et al.

George et al teach the construction of a single-chain Fv molecule with a myc-peptide tag at the N-terminal sequence of the Vh domain (please see figure 1, in particular), in addition to the binding of sFv-myc to TNP-coated cells (page 1805, column 2 in particular). George et al teach the sFv-myc bind specifically to cell surfaces and is recognized by the FITC-anti-myc peptide antibody, thus teaching that the binding affinity of the sFv to the antigen is not affected by the conjugation of small peptide sequences at the N-terminal portion of the Vh domain.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produced an antibody conjugated to a peptide molecule, wherein the antibody and the peptide molecule bind to the same target as taught by Shin and Morrison and George et al.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used produced an antibody conjugated to a peptide molecule wherein both the antibody and the peptide bind to the same target, wherein the peptide molecule is conjugated to the carboxy terminus of the CL region as taught by Shin and Morrison, because Shin and Morrison teach the expression and characterization of an antibody binding specificity joined to insulin-like growth factor 1 (IGF1) and the potential applications of such chimeric molecules for cellular targeting, in addition to teaching that the IGF1 molecule can be conjugated to the C-terminus of the of the CL region.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced an antibody conjugated to a peptide as claimed because Shin and Morrison et al teach a chimeric molecules comprising IgG3-IGF1, wherein IGF1 is an insulin-like growth factor and IgG3 is the chimeric mouse-human anti-dansyl (anti-Dns) antibody, and that the the simultaneous binding by the antibody combining sire to the antigen on the surface of the

tumor cell and by the hormone to the hormone receptor will increase the specificity of targeting.

Moreover, one of ordinary skill in the art would have known to combine the teachings of Shin and Morrison and George et al because Shin and Morrison et al teach the conjugation of an insulin-like growth factor (a 7 kDa molecule, which is less than 100 amino acids in length and can be categorized as a peptide) to the C-terminus of CL domain of IgG3 and George et al teach the construction of a single-chain Fv (sFv) molecule with a myc-peptide tag at the N-terminal sequence of the Vh domain, in addition to teaching that the sFv-myc bind specifically to cell surfaces and is recognized by the FITC-anti-myc peptide antibody, thus teaching that the binding affinity of the sFv to the antigen is not affected by the conjugation of small peptide sequences at the N-terminal portion of the Vh domain.

Thus, due to the indefinite nature of the claims and as interpreted, the teachings of Shin and Morrison and George et al read upon the claims 47-50 wherein Shin and Morrison teach the conjugation of a peptide molecule to the C-terminus of the CL domain and George et al teach the conjugation of a peptide molecule to the N-terminus of the VH domain, in addition to the binding of the antibody molecules to their specific antigens (please see the references cited, entire articles) thus showing that the antigen binding affinity of the antibody molecule is not inhibited by the conjugation of the peptide molecule at either the N-terminus of the VH molecule or the C-terminus of the CL molecule.

Therefore, the invention as a whole, as interpreted, was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

***Conclusion***

12. No claims are allowed

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

14. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER